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Toxicological Insights Gained From Cell Cultures And Other Models

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OBJECTIVE. Toxicology is an inherently predictive science in that we hope to predict whether and how much of a chemical will produce adverse effects in humans prior to release of drugs and chemicals into the marketplace. Traditionally the gold standard for pre-clinical toxicological testing is the administration of chemicals by the intended route of administration in one or more animal species. While animal studies have been extremely valuable in predicting relative safety in humans, there have been exceptions where humans have experienced adverse effects from drugs that did not appear to produce such effects in animal studies. Furthermore, the cost of animal studies increases the cost of drug development such that the 3R's (reduce, refine, replace) have become critical for the chemical and drug testing industry. Inherent in this concept is the idea that in vitro testing, particularly using human-derived materials, can eventually be adopted in place of extensive animal testing. The objective of this presentation is to familiarize clinical toxicologists with a variety of cell culture models for toxicology testing.

METHODS AND RESULTS. To replace or reduce animal usage, it was originally proposed that chemicals could be screened in parallel in a variety of cell cultures using transformed cell lines from various tissues. While cell lines might be valuable for screening, they have altered biochemistry compared to normal tissues, particularly missing normal transporters and metabolizing enzymes. Primary cells retain in vivo characteristics of tissues in culture so are often preferred. However, it is difficult to culture primary cells from most human tissues, although kidney cells are an exception. Epithelial cells, grown on plastic surfaces don't retain cellular polarity, but can be grown on microporous membrane inserts, which allow compartmentalized studies of toxicity and transport from apical and basolateral sides.

Cell cultures in 2D orientation are being replaced with cells in various 3D matrices, which allows for a more natural orientation of cell to cell interactions. So-called "spheroids" using co-culture of human hepatocytes with non-parenchymal cells such as Kupffer and stellate cells have shown retention of morphology and function that allows for human-like assessment of liver toxicity. An intriguing new approach is testing of toxicity in stem cells that are differentiated into neuronal and glials cells; co-culture of such "brain balls" allows for neurotoxicity and developmental assessments.

CONCLUSION. Novel methods of human cell culture are likely to become useful in predicting drug and chemical safety in humans.